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Award Number: DAMD17-03-1-0101

TITLE: A Novel Approach to Monitoring Prostate Tumor Oxygenation: Proton MRI of the Reporter Molecule Hexamethyldisiloxane

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REPORT DATE: March 2005

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	March 2005	Annual Summary(1 Mar 2004 - 28 Feb 2005)

4. TITLE AND SUBTITLE
A Novel Approach to Monitoring Prostate Tumor Oxygenation: Proton MRI of the Reporter Molecule Hexamethyldisiloxane

5. FUNDING NUMBERS
DAMD17-03-1-0101

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)
Growing evidence from experimental and clinical studies confirms that solid human tumors have foci of hypoxic cells, which have a profound influence on the therapeutic outcome of cancer chemotherapy and radiotherapy. A strong argument therefore exists for assessing the hypoxic fraction of tumors prior to patient treatment, and to tailor this treatment accordingly. It has been shown that there is linear relationship between R1 of hexamethyldisiloxane (HMDSO) and pO_2, and the R1 of HMDSO is insensitive to various ions and minimally sensitive to temperature. The primary sequence for in vivo T1 measurement with water and fat suppression has been established, which can successfully monitor the global tumor oxygenation responding to respiratory intervention by measuring HMDSO spin-lattice relaxation time using spectroscopy. Although the imaging technique still needs to be optimized in tumor, pO2 maps accompanying respiratory intervention has been obtained in rat muscle. So, Hexamethyldisiloxane shows promise as a reporter molecule to measure tumor oxygenation by ^1H MRS and potentially by MRI. This opens new opportunities for MR tumor oximetry, particularly since HMDSO is used widely in biomedical materials and as an ingredient in consumer products; and HMDSO is reported to have minimal toxicity.

14. SUBJECT TERMS
Hexamethyldisiloxane, hypoxia, Prostate tumor, Proton MRI, Oximetry

15. NUMBER OF PAGES
14

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction:

Growing evidence from experimental and clinical studies confirms that solid human tumors have foci of hypoxic cells, which have a profound influence on the therapeutic outcome of cancer chemotherapy and radiotherapy: the level and severity of hypoxia can be a strong prognostic factor of disease progression and survival. A strong argument therefore exists for assessing the hypoxic fraction of tumors prior to patient treatment, and to tailor this treatment accordingly.

Baseline pO_2 and dynamic changes with respiratory intervention has been measured extensively in rat prostate tumors by ^{19}F MRI (*FREDOM*, *F*luorocarbon *R*elaxometry using *E*cho planar imaging for *D*ynamic *O*xygen *M*apping) based on the spin-lattice relaxation of Hexafluorobenzene (HFB), which provides spatially resolved maps of tumor oxygenation at depth and allows monitoring of dynamic changes at specific locations. However, for clinical application ^{19}F NMR is not yet widely available. A proton MR analog of HFB could facilitate immediate widespread oximetry. We have identified hexamethyldisiloxane (HMDSO) as a potential reporter. HMDSO has extensive symmetry and a single proton resonance well removed from water.

We had three specific aims for this project:

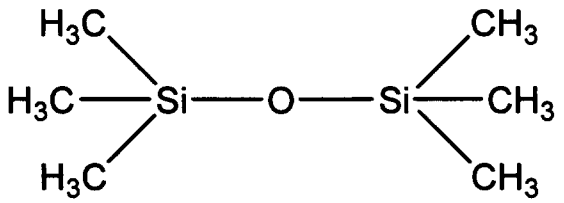
Task1. Characterize the effects of external factors on T1(spin-lattice relaxation time) of HMDSO in vitro and get the calibration curves, Month 1-6

Task2. Develop relevant MR pulse sequences with H_2O suppression for imaging. Establish experimental prostate tumor models and measure the retention time of HMDSO in tumors, Month 6-12

Task3. Make pO_2 maps and measure prostate tumor oxygen dynamics with respect to growth rate and respiratory challenge, Month 12-24

Body:

Hexamethyldisiloxane (HMDSO) is used widely in biomedical materials and as an ingredient in consumer products, such as a thin polymeric coating on suture for cardiovascular surgery, or the thin layer onto the inner surface of plasma-modified small diameter tubing, etc. HMDSO is reported to have minimal toxicity. A previous test, in vitro indicated that the spin-lattice relaxation time of HMDSO was sensitive to oxygen tension. HMDSO is highly hydrophobic, and therefore can be injected intratumorally at specific sites and will not diffuse in the tumor. Moreover, the boiling point of HMDSO is 99-100°C. In addition, HMDSO has only one ^1H signal and the chemical shift difference between HMDSO and H_2O is about 4.7ppm. Thus, we believe HMDSO may be appropriate for measuring tumor pO_2 by ^1H MRS and MRI. In this proposal, I proposed to develop proton MR techniques using this new reporter molecule, HMDSO, to assess prostate tumor oxygenation in different prostate tumor sublines with several selected levels of histological differentiation.



I completed task 1 and 2 in the first year. For the second year, my statement of work is:

Task 3. Make pO_2 maps and measure prostate tumor oxygen dynamics with respect to growth rate and respiratory challenge, Month 12-24

a. Measure baseline pO_2 of tumors and make the pO_2 map
b. Measure tumor oxygen dynamics with respiratory intervention
c. Excise and process tumor tissue for histology
d. Prepare manuscripts and reports (month 18-24)

Key research accomplishments:

Task 3a. Measure baseline pO_2 of tumors and make the pO_2 map (Dr. Vikram Kodibagkar, a MR scientist in the Department of Radiology at UTSW collaborated and assisted me in the task)

It has been reported last year that the pulse sequence (Fig1) with fat and water suppression developed by Dr. Kodibagkar worked very well with phantom. When it was used in Copenhagen rat thigh, the water and fat suppression are very effective, and baseline pO_2 map was obtained (Fig 2). However, when this pulse sequence was used in tumor, water and fat suppression was incomplete; therefore, HMDSO imaging was less satisfactory. This maybe can be ascribed to different physiological characteristics of tumor and muscle, and tumor has more fat.

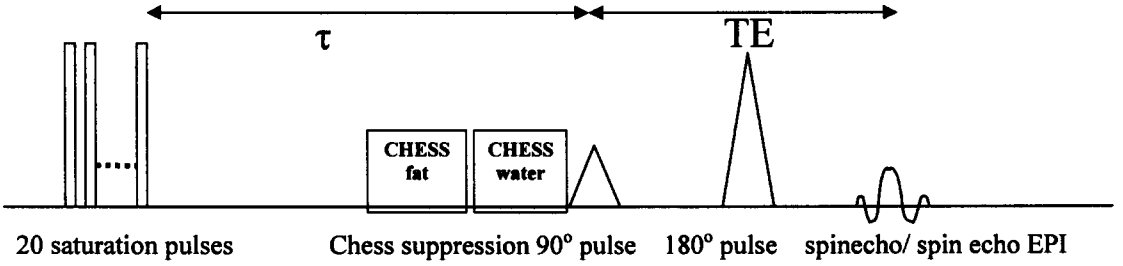


Fig 1. Pulse sequence for HMDSO relaxometry with fat and water CHESS suppression. For spectroscopy: both $\pi/2$ and π pulses are frequency selective for the HMDSO resonance. For imaging: a frequency selective $\pi/2$ and a slice selective π pulse with EPI detection are used.

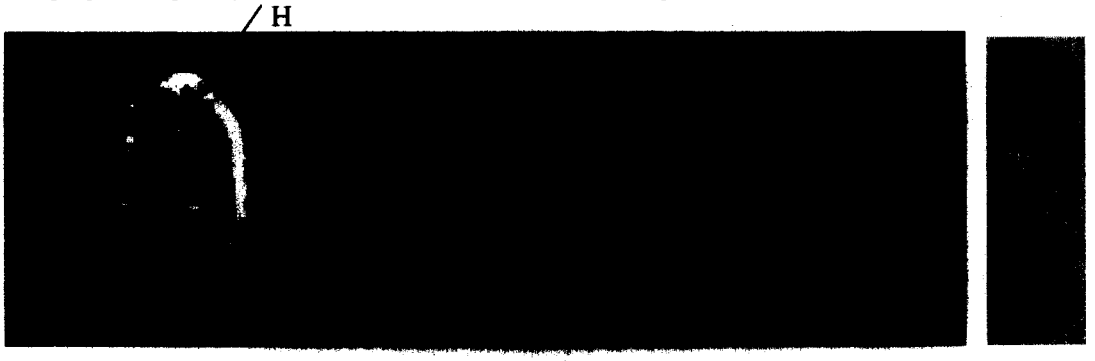


Fig 2. (a) T2 weighted spin-echo image of rat thigh showing hyperintense HMDSO (H) (b) comparative proton density weighted EPI image with fat and water suppression. (c) Corresponding pO_2 map showing a mean $pO_2 = 125 \pm 20$ torr

Task 3b. Measure tumor oxygen dynamics with respiratory intervention

I. As a proof or principle, the global oxygen dynamics curve (Fig 3) and pO_2 maps (Fig4) responding to respiratory challenge was successfully measured by the developed pulse sequence in rat thigh muscle. During the experiment, the rat was breathing air- oxygen- air.

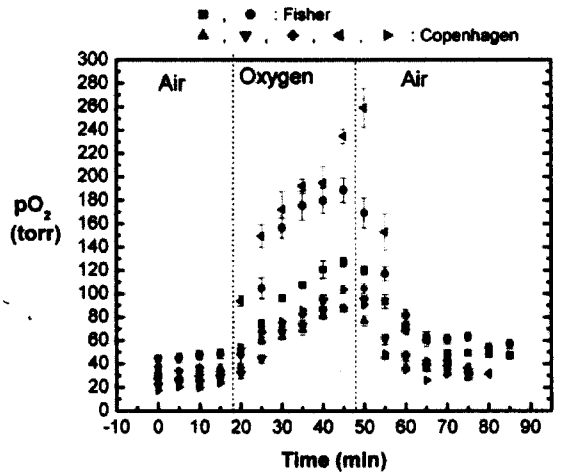


Fig3. Rat thigh muscle oxygen dynamics with respect to respiratory intervention (7 individual investigations in 2 rat strains)

Air(35±7torr) 15 min O2(77±8) 30 min O2(134±43) 15 min air(44±15) 30 min air(37±9)

Fig 4. Rat thigh muscle pO_2 map with respect to respiratory intervention

II: We measured the global tumor oxygen dynamics using frequency selective spectroscopy for the HMDSO resonance (Fig1). 120 μl HMDSO was injected intratumorly using 32 gauge Hamilton needle to distribute in the peripheral region of the AT1 tumor. MRI studies were performed on a Varian 4.7 T system. During the experiment, the rat breathed air (15min)- oxygen (30min)- air (20min) (tumor 62R2L2 is exceptional, 10min air-25min oxygen- 15min air). Fig 5 showed the pO_2 value for each tumor with respect to the breathing sequence. Table 1 and Fig 6 showed average pO_2 values for air-oxygen-air.

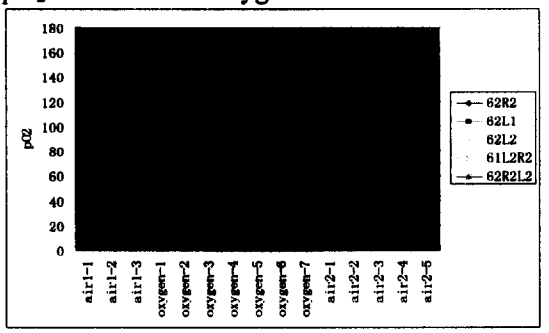


Fig5. Tumor oxygen dynamics with respect to respiratory intervention for rat prostate AT1 tumor

Table1. Global tumor oxygen dynamics with respiratory intervention

Tumor size(cm3)		Air	oxygen	air
1.5x1.5x1.0	**R1**	0. 1825	0. 1963	0. 1879
	pO_2	36	44	39
	SD	10. 9	8. 8	13. 0
1.4X1.7X2.0	**R1**	0. 175	0. 2146	0. 1814
	pO_2	32	55	35
	SD	17. 5	16. 7	7. 7
1.5x1.3x1.0	**R1**	0. 194	0. 2459	0. 2255
	pO_2	43	73	61
	SD	3. 7	10. 8	34. 2
1.6x1.4x1.3	**R1**	0. 1624	0. 1865	0. 1889
	pO_2	25	38	40
	SD	1. 2	8. 4	4. 2
1.4x1.2x0.8	**R1**	0. 2436	0. 3566	0. 271
	pO_2	71	123	87
	SD	36	29	49

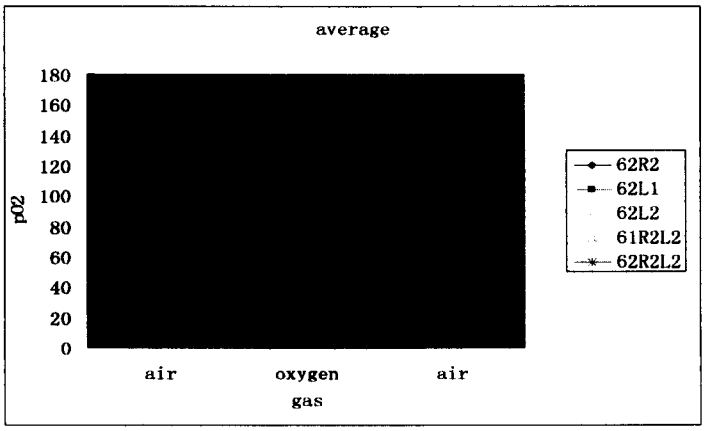


Fig6. The average pO_2 value during respiratory intervention

III. Oximetry based on HMDSO imaging in tumor is still under development. It is more difficult to implement than in muscle. While continuing to tackle this problems, I have explored application of BOLD (Blood Oxygen Level Dependent) imaging in Dunning prostate rat tumor. During the experiment, the rat was breathing 15min air-25min oxygen- 20min air. The data were normalized using the initial intensity. Fig 7 shows the signal intensity changed with gas challenge for individual data point. Table 2 and Fig 8 shows average values for air-oxygen-air.

Table 2. Normalized BOLD imaging intensity with respiratory intervention

Tumor number	**60R1**	**61R2**	**60R2L2**	**60R1L1**
Tumor size (cm3)	1.7x1.8x1.6	2.4x2.2x1.8	2.1x1.9x1.6	2.3x2.1x1.9
Respiratory intervention	The normalized signal intensity average			
Air	0.991573	0.998785	0.996979	0.992108
Oxygen	0.991994	1.016408	1.001964	1.051556
Air	1.024228	0.983706	0.994902	1.063712

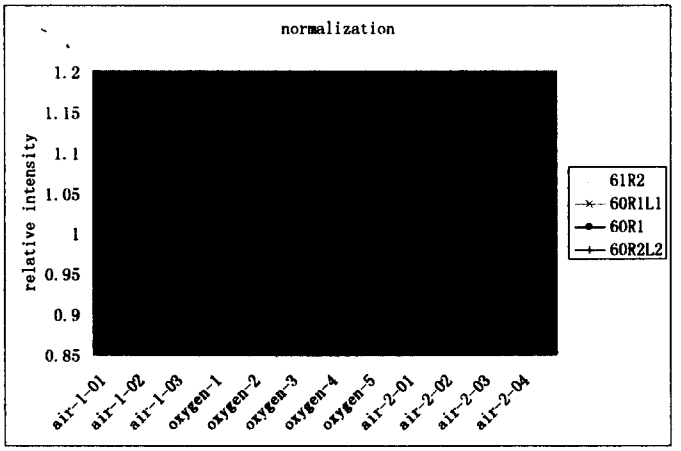


Fig 7. BOLD imaging signal intensity for AT1 tumor

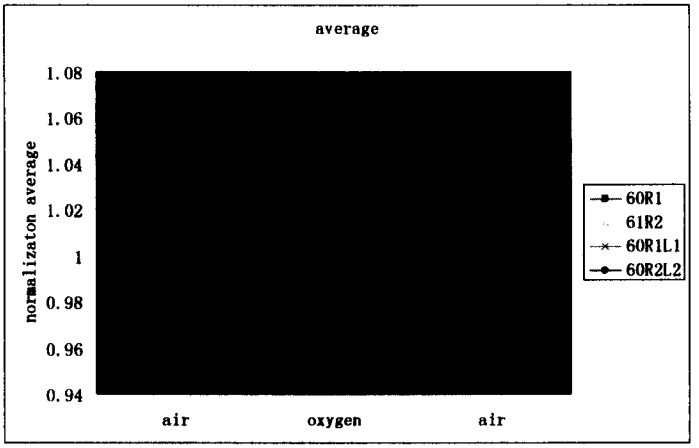


Fig 8. BOLD imaging averaged signal intensity for AT1 tumor

I am continuing analysis particularly to examine original heterogeneity.

Task 3c. Excise and process tumor tissue for histology

The tumor tissues for above experiments were frozen and stored. However, the histology has not been done yet. This task will be finished in 2005 during the approved 1 year no cost extension

.

Task 3d. Prepare manuscripts and reports

A manuscript describing measurement of tumor oxygenation with HMDSO as a reporter molecule is under preparation.

Reportable outcomes:

One abstract describing work supported by this grant has been presented as poster at Society for Molecular Imaging , Sep 2004.

A New Frontier for Proton MRI: Quantitative Tissue Oximetry, Vikram D. Kodibagkar, **Weina Cui**, Ralph P. Mason. SMI, St. Louis, Sep 2004

A second abstract describing work supported by this grant will be presented as poster at the International Society of Magnetic Resonance in Medicine on May 2005.

Quantitative Tissue Oximetry using Proton MR of Hexamethyldisiloxane. Vikram D. Kodibagkar, **Weina Cui**, Metthew. Merritt and Ralph P. Mason, ISMRM, Miami, May 2005

Conclusions:

The above experiments showed that: 1) As a imaging technique, it has been proved that the chemical shift select imaging of HMDSO with water and fat suppression can successfully measure the oxygen tension in rat muscle and tumor; 2) the developed pulse sequence can successfully monitor the rat thigh muscle oxygen dynamics; 3) HMDSO spin-lattice relaxation time (T1) in tumor responds to respiratory intervention (air-oxygen-air); 4) BOLD imaging signal intensity in tumor also responds to respiratory intervention (air-oxygen-air). So, Hexamethyldisiloxane shows promise as a reporter molecule to measure tumor oxygenation by ^{1}H MRS and potentially by MRI. This opens new opportunities for MR tumor oximetry, particularly since HMDSO is used widely in biomedical materials and as an ingredient in consumer products; and HMDSO is reported to have minimal toxicity.

Quantitative Tissue Oximetry using Proton MR of Hexamethyldisiloxane

V. Kodibagkar, W. Cui, M. Merritt and R. P. Mason

Synopsis

There is increasing evidence for the importance of tissue oxygenation in development, progression, and response to cancer therapy. Thus, the opportunity to measure tissue oxygen tension (pO_2) non-invasively may be significant in understanding mechanisms of tissue function and in clinical prognosis. The linear dependence of the spin lattice relaxation rate, R1, of the ^{19}F NMR resonances of fluorocarbons on pO_2 is well known and has been studied extensively. We recently presented hexamethyldisiloxane (HMDSO) as a potential analogous ^{1}H NMR pO_2 reporter molecule . HMDSO has a single proton NMR resonance, which is ideal for imaging. 1H MRI of reporter molecules is subject to potential interference from the large water and fat resonances, but the chemical shift of –5 ppm relative to water allows chemical shift selective imaging. We now demonstrate application with bulk pO_2 measurements and pO_2 maps obtained *in vivo* in rat thighs and tumors following a direct intra tissue injection of 100 µl HMDSO. Dynamic changes in pO_2 were assessed with respect to respiratory challenge. Given the minimal toxicity and ready availability of HMDSO, we believe it has great potential for ultimate application as a pO_2 reporter molecule in the clinic.

Introduction: **There is increasing evidence for the importance of tissue oxygenation in development, progression, and response to cancer therapy. Oxygen is required for efficient function by most tissues and hypoxia leads to rapid cellular dysfunction and damage. In addition, hypoxic tumor cells are refractory to radiotherapy. Thus, the opportunity to measure tissue oxygen tension (pO_2) non-invasively may be significant in understanding mechanisms of tissue function and in clinical prognosis. The linear dependence of R_1 of fluorocarbon ^{19}F resonances on pO_2 is well known and has been studied extensively[1]. We have previously studied the potential of HMDSO as a ^1H based pO_2 reporter molecule and found the linear dependence of R_1 of HMDSO on pO_2 (R_1= 0.12+ 0.00173*pO_2[torr] at 37°C). Here, we study the modulation of tissue oxygenation in response to oxygen challenge in order to further validate the use of HMDSO as a pO_2 reporter molecule.**

Materials and Methods: **A spin-echo EPI based pulse sequence was used for imaging and measuring T_1 values using a Varian 4.7 T scanner. The sequence consisted of a) 20 non-selective saturation pulses followed by a delay *tau* for magnetization recovery, b) 3 CHESS pulses for selective saturation of water and fat immediately followed by c) spin-echo EPI detection with a slice selective 90° pulse and a frequency selective 180° pulse. T_1 maps were obtained using this sequence with the ARDVARC (*A*lternating *R*elaxation *D*elays with *V*ariable *A*cquisitions for *R*eduction of *C*learance effects) protocol[2], by varying *tau* (3 and half min. per T1 measurement). For comparison, reference images were obtained using a spin echo sequence. T_1 and pO_2 maps were computed using homebuilt software based on the Matlab programming language.**

Results and Discussion:

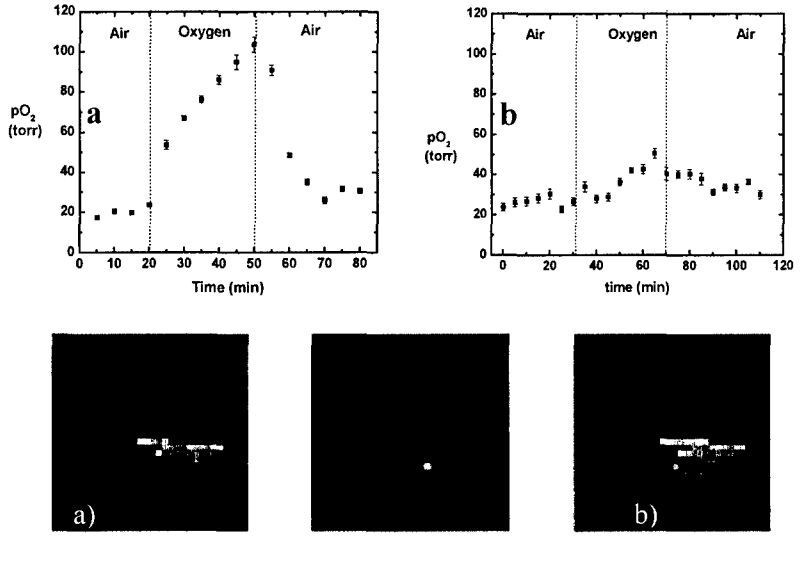


Fig1: *Monitoring modulation of tissue oxygenation by bulk spectroscopy in* ***a)*** *healthy rat thigh and* ***b)*** *rat Dunning prostate AT1 tumor (volume: 5.8 cc)*

Fig2: *Monitoring modulation of tissue oxygenation in response to oxygen challenge in healthy rat thigh* ***a)*** *Air breathing,* ***b)*** *after breathing oxygen for 30 min and* ***c)*** *30 min after reverting to air*

Modulation of tissue oxygenation in response to oxygen challenge was successfully monitored by bulk spectroscopy and imaging. The short total acquisition time reveals dynamic response to therapeutic interventions. Minimal toxicity and wide availability add to the promise of HMDSO as a pO_2 reporter molecule. We believe it has great potential for application in the clinic especially as all the techniques used can be implemented on clinical scanners.

Acknowledgements: **This work was supported by DOD DAMD17-03-1-0101, Cancer Imaging Program P20 CA086354 and BTRP P41 RR02584**

References

(1) Zhao, D.; Jiang, L.; Mason, R. P. *Methods Enzymol* **2004**, *386*, 378-418.

(2) Hunjan, S.; Zhao, D.; Constantinescu, A.; Hahn, E. W.; Antich, P. P.; Mason, R. P. *Int. J. Radiat. Oncol. Biol. Phys.* **2001**, *49*, 1097-1108.

A new frontier for proton MRI: quantitative tissue oximetry

V. Kodibagkar, W. Cui, and R. P. Mason

There is increasing evidence for the importance of tissue oxygenation in development, progression, and response to cancer therapy. Thus, the opportunity to measure tissue oxygen tension (pO_2) non-invasively may be significant in understanding mechanisms of tissue function and in clinical prognosis. The linear dependence of the spin lattice relaxation rate, R_1, of the ^{19}F NMR resonances of fluorocarbons on pO_2 is well known and has been studied extensively. However, proton MR is far more readily available. We now present hexamethyldisiloxane (HMDSO) as a 1H NMR based pO_2 reporter molecule.
HMDSO has a single proton NMR resonance, which is ideal for imaging. It is highly hydrophobic interacting with dissolved gases, but not metal ions. We have found a linear response: $R_1 = 0.13 + 0.00175 * pO_2$[torr] at 37 °C and 4.7 T. 1H MRI of reporter molecules is subject to potential interference from the large water and fat resonances, but the chemical shift of –5 ppm relative to water allows chemical shift selective imaging. We have implemented a spin-echo EPI based pulse sequence for imaging and measuring T_1 values. The sequence comprises a train of 20 non-selective 90° pulses for saturation of signal followed by a delay τ for magnetization recovery. Three CHESS pulses provide frequency selective saturation of water and fat immediately followed by spin-echo EPI detection with a slice selective 90° pulse and a frequency selective 180° pulse. pO_2 maps were obtained in vivo in rat tumors in 21/2 mins following direct intra tumoral injection of 100 μl. Most significantly dynamic changes in pO_2 were assessed with respect to interventions (*e.g.*, respiratory challenge). Given the minimal toxicity and
ready availability of HMDSO, we believe it has great potential for ultimate application as a pO_2 reporter molecule in the clinic.
This work was supported by NCI Pre-ICMIC P20 CA086354 and DOD DAMD17-03-1-0101

A New Frontier for Proton MRI: Quantitative Tissue Oximetry

Vikram D. Kodibagkar, Weina Cui, Ralph P. Mason.
Cancer Imaging Program, Department of Radiology
The University of Texas Southwestern Medical Center at Dallas, Dallas TX

Introduction

- There is increasing evidence for the importance of tumor oxygenation in development, progression, and response to therapy
- Oxygen is required for efficient function by most tissues and hypoxia leads to rapid cellular dysfunction and damage.
- In addition, hypoxic tumor cells are refractory to radiotherapy.
- Thus, the opportunity to measure tissue oxygen tension (pO_2) non-invasively may be significant in understanding mechanisms of tissue function and in clinical prognosis

MRI relaxometry to study oxygen tension in tissue

- The linear dependence of R1 of fluorocarbon ^{19}F NMR resonances on pO_2 is well known and has been studied extensively (1,2)
- Previous studies in our lab used intra-tumoral injection of the reporter molecule hexafluorobenzene (HFB) (1-3). Oximetry was performed using pulse-burst saturation-recovery and spin-echo EPI detection
- A ^1H MRI pO_2 reporter-molecule would greatly help translation of the MR oximetry method to clinical studies

We have now studied the potential of HMDSO as a ^1H based pO_2 reporter molecule.

^1H MRI pO_2 reporter: Hexamethyldisiloxane (HMDSO)

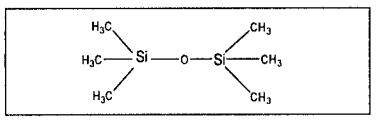


Figure 1

- Symmetric molecule with a single proton resonance
- Chemical shift close to TMS (0 ppm) well separated from the water resonance
- Negligible toxicity

Linear dependence of R1 of HMDSO on pO_2

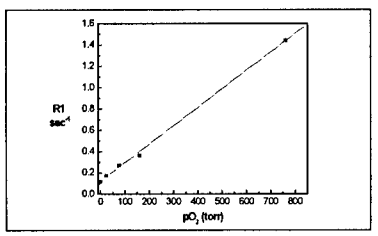


Figure 2
The ^1H spin lattice relaxation rate R1 of HMDSO varies linearly with oxygen tension (pO_2). At 40 °C, R1 = 0.12 + 0.00173* pO_2 (torr)

Acknowledgements:

This work was supported by a post doctoral fellowship from the DOD Prostate Cancer Initiative (DAMD17-03-1-0101,WC) in conjunction with the Cancer Imaging Program (NCI Pre-ICMIC P20 CA086354) The MR investigations were performed at the Mary Nell and Ralph B Rogers NMR Center, an NIH BRTP facility (#P41RR02584)

Minimal Temperature Dependence

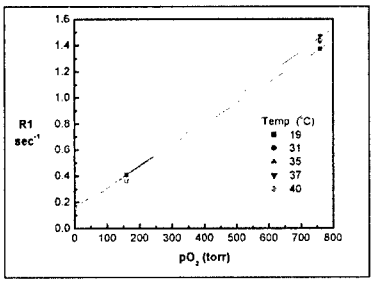


Figure 3
At 4.7 T, there is minimal dependence on temperature in the physiologically relevant range 20- 40 °C

In vivo relaxometry by imaging/ spectroscopy: pulse sequence

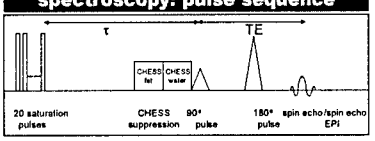


Figure 4
Pulse sequence for HMDSO relaxometry with fat and water CHESS* suppression. For spectroscopy: both 90° and 180° pulses are frequency selective for the HMDSO resonance.
For imaging: a frequency selective 90° and a slice selective 180° pulse with EPI detection are used.

In vivo relaxometry by imaging/ spectroscopy: Methods

- MRI studies were performed on a Varian 4.7 T system. T1 values/maps were obtained using the ARDVARC (Alternating Relaxation Delays with Variable Acquisitions for Reduction of Clearance effects) protocol (1), by varying τ.
- Imaging phantom comprised a water filled tube containing smaller tubes filled with mineral oil and HMDSO
- For *in vivo* spectroscopy studies, 50 µl HMDSO was injected directly into a Dunning prostate R3327-AT1 tumor on a male Copenhagen rat using 32 gauge Hamilton needle
- For *in vivo* imaging studies, 100 µl HMDSO was injected subcutaneously into thigh of Copenhagen rat

For further information, you may contact Dr. Kodibagkar at: vikram.kodibagkar@utsouthwestern.edu

In vivo spectra

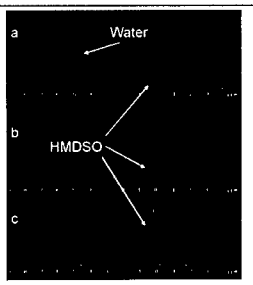


Figure 5
***In vivo* ^1H NMR spectra from Dunning prostate AT1 tumor on the foreback of Copenhagen rat injected with HMDSO.**
a) Spin echo using nonselective pulses
b) Spin echo using selective pulses and CHESS water suppression
c) (b) X 20

Relaxometry by spectroscopy

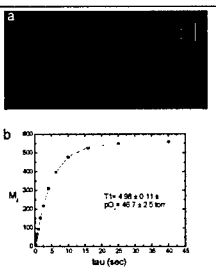


Figure 6
***In vivo* ^1H HMDSO T1 measurement from Dunning prostate AT1 tumor.**
(a) Spectra corresponding to different τ values used to measure T1. The spectral window is –2 to 6 ppm showing no water or fat signal at any tau values
(b) Magnetization recovery curve from (a)

Modulation of tumor oxygenation

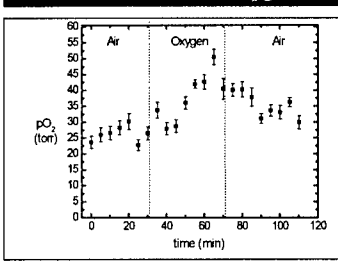


Figure 7
Monitoring changes in tumor oxygenation *in vivo* with respect to oxygen challenge in AT1 tumor (volume = 5.8 cm^3). Response closely matches that reported previously using HFB (1,2)

Efficient water and fat suppression

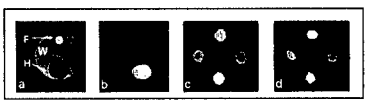


Figure 8
(a) T1 weighted spin-echo image of phantom with smaller tubes containing mineral oil (F) and HMDSO (H) inside a tube containing water (W) and
(b) proton density weighted EPI image of the same phantom with fat and water suppression

T1 maps of a second phantom containing HMDSO saturated with gases with varying concentrations of oxygen obtained by
(c) spin-echo sequence and
(d) the spin-echo EPI sequence

In vivo Imaging

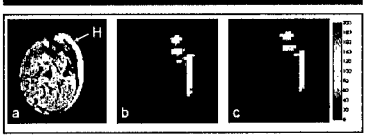


Figure 9
a) T2 weighted spin-echo image of rat thigh showing hyperintense HMDSO (H)
b) comparative proton density weighted EPI image with fat and water suppression
c) Corresponding pO_2 map showing a mean pO_2 = 125±20 torr.

Results

Spectroscopy:

- The spin-lattice relaxation rate R1 of HMDSO showed a linear dependence on pO_2 : **R1= 0.12 + 0.00173*pO_2 (torr)**
- Minimal temperature dependence was observed in the temperature range 20-40 °C
- Effective suppression of water and fat resonances was achieved in phantom and rat prostate tumor at all τ values
- Dynamic response of tumor pO_2 to oxygen challenge was studied

Imaging:

- Effective fat and water suppression was obtained in phantom and rat thigh
- The entire T1 data set with 14 τ values (spanning 0.05 to 40 s) was obtained within 2 ½ minutes.

Conclusions

- Hexamethyldisiloxane (HMDSO) is shown to be a promising pO_2 reporter molecule for ^1H MRI.
- Relaxometry of HMDSO was demonstrated with efficient fat and water suppression using frequency selective excitation and suppression
- This approach is tailored towards future *in vivo* applications and the short total acquisition time will allow us to monitor dynamic response to interventions
- Minimal toxicity and wide availability add to the promise of HMDSO as a pO_2 reporter molecule.

References

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